PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

[71] Applicant: HOECHST AKTIENGESELLSCHAFT
Address: D-6230 FRANKFURT/MAIN 80, FEDERAL REPUBLIC OF GERMANY

[70] Nominated Person: HOECHST AKTIENGESELLSCHAFT
Address: D-6230 FRANKFURT/MAIN 80, FEDERAL REPUBLIC OF GERMANY

[54] Invention Title: ADSORBATE OF AN AUXILIARY MIXTURE AND A NON-SOLID ACTIVE COMPOUND FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS

[72] Name(s) of actual inventor(s): THEOPHIL HORNYKIEWYTSCH

[74] Address for service in Australia: c/o WATERMARK PATENT & TRADEMARK ATTORNEYS, of The Atrium, 290 Burwood Road, Hawthorn, Victoria 3122, Australia

BASIC CONVENTION APPLICATION(S) DETAILS

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Basic Applicant(s): HOECHST AKTIENGESELLSCHAFT

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By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

Darryl B. Mischlewski
Registered Patent Attorney

DATED this 9th day of September 1993.
Title

ADSORBATE OF AN AUXILIARY Mixture AND A NON-SOLID ACTIVE COMPOUND FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS

International Patent Classification(s)

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Applicant(s)

HOECHST AKTIENGESELLSCHAFT

Inventor(s)

THEOPHIL HORNykiewYtsch

Attorney or Agent

WATERMARK PATENT & TRADEMARK ATTORNEYS, Locked Bag 5, HAWTHORN VIC 3122

Claim

1. An adsorbate comprising a pyridine-2,4-dicarboxylic acid N,N'-diamide as the active compound, 10-30% of highly disperse silica, 50 to 70% of an inert auxiliary and 0 to 30% of starch and, if appropriate, other additives.

3. A process for the preparation of an adsorbate, which comprises initially introducing a mixture of 10-30% of highly disperse silica, 50-70% of inert auxiliary and 0 to 30% of starch and adding an aqueous solution of a pyridine-2,4-dicarboxylic acid N,N'-diamide to this mixture and optionally converting the homogeneous adsorbate obtained into a suitable administration form.

N,N'-(3-Methoxypropyl)-pyridine-2,4-dicarboxamide (also known as HOE 277), like the other diamides described in EP 0,409,119, is a highly viscous, tacky substance at room temperature, which is strongly hygroscopic. Pyridine-2,4-dicarboxamides inhibit proline hydroxylase and lysine hydroxylase and are suitable as fibrosuppressants and immunosuppressants (EP 0,409,119).
Application Number:

Lodged:

Invention Title: ADSORBATE OF AN AUXILIARY MIXTURE AND A NON-SOLID ACTIVE COMPOUND FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS

The following statement is a full description of this invention, including the best method of performing it known to :-US
DESCRIPTION

Adsorbate of an auxiliary mixture and a non-solid active compound for the preparation of pharmaceutical compositions

N,N’-(3-Methoxypropyl)-pyridine-2,4-dicarboxamide (also known as HOE 277), like the other diamides described in EP 0,409,119, is a highly viscous, tacky substance at room temperature, which is strongly hygroscopic. Pyridine-2,4-dicarboxamides inhibit proline hydroxylase and lysine hydroxylase and are suitable as fibrosuppressants and immunosuppressants (EP 0,409,119).

The object was to process HOE 277 to give tablets for administration to humans using pharmaceutically customary auxiliaries. The format of the tablets should be chosen such that it is also still accepted by patients on the international scale, for example even in Japan. The maximum dimensions prescribed were 15 x 7 mm. The dose should be about 50-100 mg per tablet.

Said substance properties of HOE 277 are very unfavorable for the preparation of tablets and lead, when using a normal recipe and preparation process as is given in pharmaceutical technology handbooks, to a number of difficulties. Inter alia, HOE 277 adhered very strongly to the wall of the apparatus used, for example the mixer.

HOE 277 formed a solid crust on the wall, which was difficult to break down mechanically, with the auxiliaries used. Agglomerate formation in the active compound-auxiliary mixtures or granules led to inhomogeneities of the tablets prepared therefrom. The tablet cores pressed from the granules had only a low hardness and were therefore not very suitable for film-coating. Film-coating is necessary to mask the bitter taste of the active compound and to protect it from the direct action of light.
The absorption of active compounds on highly disperse SiO₂ has already been repeatedly described (for example EP-B-0,158,120, EP-A-487,335, US Patent 2,879,161, J. Pharm. Sci. 61, 1430 (1972) and J. Pharm. Sci. 73, 401 (1984)). As a rule, this is carried out to increase the solubility of poorly soluble active compounds by increasing the surface area. Two processes for this are described. Either highly disperse SiO₂ is added with stirring to a solution of the active compound until the solution has been completely absorbed by the solid. The solvent can then be removed by drying. Alternatively, the active compound is mixed with the SiO₂ in a suitable mixer and in this way absorbed as homogeneously as possible on the SiO₂.

The two processes cannot be used owing to the particular properties of HOE 277. The stirring of SiO₂ into a solution of HOE 277 in water led to the formation of a pasty mass, which adhered tenaciously to the apparatus and could no longer be stirred.

The addition of HOE 277 in undiluted form or in aqueous solution to initially introduced SiO₂ leads immediately to the formation of agglomerates or of crusts on the mixing implement and container wall.

We have now found that these difficulties can be overcome if a mixture of 10-30% of highly disperse SiO₂, 50-70%, for example, of lactose and 0-30%, for example, of cornstarch is initially introduced and the active compound solution is slowly added.

The invention therefore relates to an adsorbate comprising a pyridine-2,4-dicarboxylic acid N,N’-diamide as the active compound, 10-30% of highly disperse silica, 50 to 70% of an inert auxiliary and 0 to 30% of starch.
The adsorbate is suitable for the preparation of pharmaceutical compositions.

The invention further relates to a process for the preparation of an adsorbate, which comprises initially introducing a mixture of 10-30% of highly disperse silica, 50-70% of inert auxiliary and 0-30% of starch and adding an aqueous solution of a pyridine-2,4-dicarboxylic acid N,N'-diamide to this mixture and optionally converting the homogeneous adsorbate obtained into a suitable administration form.

The percentage data are percentages by weight. The active compound is preferably HOE 277.

The highly disperse SiO₂ particularly has a surface area between 150-400 m²/g and a mean size of the primary articles of 6 to 16 nanometers. Pharmaceutically suitable inert auxiliaries are, for example, cellulose and modified cellulose derivatives, sugars, sugar alcohols, Ca phosphates and Ca carbonate, in particular lactose.

Suitable starches are, for example, cornstarch, modified cornstarch, rice starch, potato starch and wheat starch. The SiO₂ content should be kept as low as possible because of the volume and the other technologically critical properties of the SiO₂; a ratio of 1:1 with the active compound HOE 277 proved to be adequate. The homogeneous adsorbate preferably contains 1-30% of active compound.

A homogeneous adsorbate can be prepared by stepwise addition of a concentrated active compound solution (8 mg of HOE 277 + 2 mg of H₂O). This can be poured into hard gelatin capsules or processed further to give tablets or film tablets.
In the preparation of the adsorbate according to the invention, the customarily unpleasant properties of the active compounds are positively used, i.e. the tacky, viscous active compound has the function of a binder in concentrated, aqueous solution.

It has proven advantageous for the properties of the granules and the tablets during conversion into an administration form optionally to admix in dry form an actual binder, for example polyvinylpyrrolidone, modified or pregelatinized starch, cellulose derivatives, for example methyl-, hydroxypropyl- or carboxymethyl-cellulose, polyethylene glycols, to the homogeneous adsorbate and then to prepare the final granules by addition of the amount of water which is still lacking.

A drying operation can be saved by means of the process described. This is advantageous for reasons of time and energy saving.

In order to prepare tablet cores having adequate hardness and rapid disintegration, it is necessary to dry the moist granules at high temperature to about 10-20% rel. humidity before pressing. In the outer phase, the tablet hardness can be distinctly increased during dusting by the addition of about 5% of microcrystalline cellulose. A further addition (more than 10%) leads to no further improvement.

On account of the bitter taste of the active compound, the tablets prepared from the adsorbate, optionally after granulation, customarily receive a coating film. The coating film consists, for example, of a commercially available film-forming agent, a plasticizer, a pigment and a covering substance.

After the film-coating, an unusual increase in the hardness of about 50% is again observed, which remains without negative effect on the disintegration time.
The hardness of tablet cores comprising HOE 277 prepared according to the invention was determined using an Erweka hardness-measuring apparatus. The hardness of the film tablets was also determined according to Examples 1 and 2. The mean values of 10 determinations are shown below.

<table>
<thead>
<tr>
<th>Dose</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness</td>
<td>39 N</td>
<td>52 N</td>
</tr>
<tr>
<td>Hardness of film tablets</td>
<td>61 N</td>
<td>71 N</td>
</tr>
</tbody>
</table>

Purified water is used as the granulating auxiliary, and also as a solvent or suspending medium for the active compound and the constituents of the film covering and is not a constituent of the finished composition.

2., 3. and 4. are mixed. A concentrated, aqueous solution of 1. is added stepwise to this mixture. The adsorbate is mixed dry with 5., 6., 7. and 8. and, after addition of water, granulated moist and pressed to give tablet cores. These are then coated with a film covering.
Example 1: 40 mg HOE 277 film tablets

Composition of a dose unit

<table>
<thead>
<tr>
<th>Substance</th>
<th>Amount in the individual dose [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HOE 277</td>
<td>40.000</td>
</tr>
<tr>
<td>2. Highly disperse silica</td>
<td>40.000</td>
</tr>
<tr>
<td>3. Lactose</td>
<td>80.000</td>
</tr>
<tr>
<td>4. Cornstarch</td>
<td>30.000</td>
</tr>
<tr>
<td>5. Polyvinylpyrrolidone</td>
<td>10.000</td>
</tr>
<tr>
<td>6. Sodium starch glycolate</td>
<td>8.000</td>
</tr>
<tr>
<td>7. Microcrystalline cellulose</td>
<td>10.000</td>
</tr>
<tr>
<td>8. Magnesium stearate</td>
<td>2.000</td>
</tr>
<tr>
<td>Film covering</td>
<td>5.000</td>
</tr>
</tbody>
</table>

225.000
Example 2: 80 mg HOE 277 film tablets
Composition of a dose unit

<table>
<thead>
<tr>
<th>Substance</th>
<th>Amount in the individual dose [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HOE 277</td>
<td>80.000</td>
</tr>
<tr>
<td>2. Highly disperse silica</td>
<td>80.000</td>
</tr>
<tr>
<td>3. Lactose</td>
<td>160.000</td>
</tr>
<tr>
<td>4. Cornstarch</td>
<td>60.000</td>
</tr>
<tr>
<td>5. Polyvinylpyrrolidone</td>
<td>20.000</td>
</tr>
<tr>
<td>6. Sodium starch glycolate</td>
<td>16.000</td>
</tr>
<tr>
<td>7. Microcrystalline cellulose</td>
<td>20.000</td>
</tr>
<tr>
<td>8. Magnesium stearate</td>
<td>4.000</td>
</tr>
<tr>
<td>Film covering</td>
<td>10.000</td>
</tr>
<tr>
<td></td>
<td>450.00</td>
</tr>
</tbody>
</table>

Purified water is used as the granulating auxiliary, and also as a solvent or suspending medium for the active compound and the constituents of the film covering and is not a constituent of the finished composition. Preparation is carried out as described in Example 1.
Example 3: 40 mg HOE 277 film tablets
Composition of a dose unit

<table>
<thead>
<tr>
<th>Substance</th>
<th>Amount in the individual dose [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HOE 277</td>
<td>40.000</td>
</tr>
<tr>
<td>2. Highly disperse silica</td>
<td>40.000</td>
</tr>
<tr>
<td>3. Lactose</td>
<td>220.000</td>
</tr>
<tr>
<td>4. Cornstarch</td>
<td>70.000</td>
</tr>
<tr>
<td>5. Polyvinylpyrrolidone</td>
<td>20.000</td>
</tr>
<tr>
<td>6. Sodium starch glycolate</td>
<td>16.000</td>
</tr>
<tr>
<td>7. Microcrystalline cellulose</td>
<td>20.000</td>
</tr>
<tr>
<td>8. Magnesium stearate</td>
<td>4.000</td>
</tr>
<tr>
<td>Film covering</td>
<td>10.000</td>
</tr>
</tbody>
</table>

Purified water is used as the granulating auxiliary, and also as a solvent or suspending medium for the active compound and the constituents of the film covering and is not a constituent of the finished composition. Preparation is carried out analogously to Example 1. The film tablets according to Examples 1 to 3 are stable.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An adsorbate comprising a pyridine-2,4-dicarboxylic acid N,N'-diamide as the active compound, 10-30% of highly disperse silica, 50 to 70% of an inert auxiliary and 0 to 30% of starch and, if appropriate, other additives.

2. An adsorbate comprising N,N'-(3-methoxypropyl)-pyridine-2,4-dicarboxamide as the active compound, 10-30% of highly disperse silica, 50 to 70% of lactose and 0 to 30% of cornstarch.

3. A process for the preparation of an adsorbate, which comprises initially introducing a mixture of 10-30% of highly disperse silica, 50-70% of inert auxiliary and 0 to 30% of starch and adding an aqueous solution of a pyridine-2,4-dicarboxylic acid N,N'-diamide to this mixture and optionally converting the homogeneous adsorbate obtained into a suitable administration form.

4. The process as claimed in claim 3, wherein the actual binder is admixed to the homogeneous adsorbate, then the mixture is granulated moist and the granules are dried.

DATED this 9th day of September 1993.

HOECHST AKTIENGESELLSCHAFT
Abstract

Adsorbate of an auxiliary mixture and a non-solid active compound for the preparation of pharmaceutical compositions

An adsorbate comprising a pyridine-2,4-dicarboxylic acid N,N'-diamide as the active compound, 10-30% of highly disperse silica, 50 to 70% of an inert auxiliary and 0 to 30% of starch and, if appropriate, other additives, and a process for the preparation of this adsorbate are described.